Warehouse for storage of raw materials, packaging materials and finished product is located at:

[redacted]

Control laboratories for testing of raw materials, intermediates and finished products is located at:

[redacted]

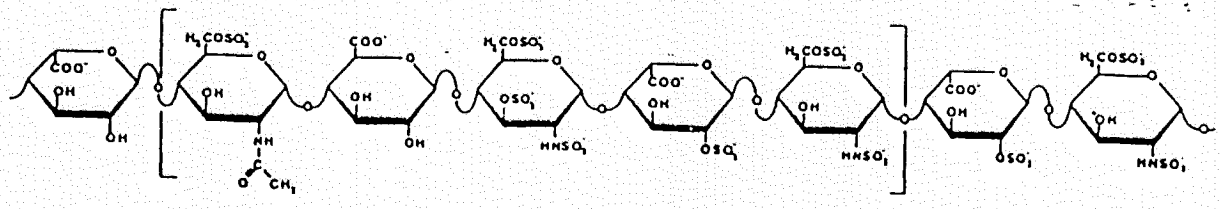
Control laboratories for testing of packaging materials is located at:

[redacted]

The finished product will be shipped to the United States from Kabi Pharmacia, AB, Sweden and marketed for hospital use, by order from a licensed physical and under the direct supervision of a licensed physical. As such the product will therefore be used and disposed of in a hospital setting. Hospitals have processes and procedures in place to deal with use and disposal of hypodermic needles and syringes in compliance with local, state and federal laws and regulations. The environment present and adjacent to various hospitals throughout the United States vary extensively and as such it is not possible to give this information.

Item 5.) Identification of Chemical substances that are the subject of the proposed action;

Low molecular weight heparin is obtained from heparin, a natural occurring substance found in the human body and in animal intestines and lungs in high concentrations. Heparin is obtained from animal tissues by various protein fractionation and purification procedures. Heparin is composed of a polysaccharide built up from disaccharides made up of alternating uronic acid and glucosamine unites. Below is the structure of a heparin octasaccharide sequence that shows most of the variously substituted monosaccharides identified to date. The pentasaccharide sequence in brackets represents the antithrombotic-binding region of heparin. It is also this region that is thought to account for the activity of low molecular weight heparins, namely by binding to antithrombin it potentiates, preferentially the inhibition of coagulation Factor Xa and only slightly affects thrombin inhibition and clotting time.



Low molecular weight heparins, in principal can be produced in two different ways. Either by enrichment of "natural" low molecular material in standard heparin or by depolymerization of heparin. Enrichment procedures involve fractional precipitation of heparin by such substances as ethanol and or chromatographic techniques such as gel filtration. Methods have been developed for controlled chemical depolymerization of heparin. Nitrous acid depolymerization of heparin is used commonly, and is the procedure described in this NDA. Other methods have been tried, such as depolymerization of the benzylic ester of heparin by ß-elimination and methods using peroxides. Enzymatic depolymerization of heparin using heparinase is another possible method. Scheme 1 on the following page is an over view of Kabi's production method.

DRUG SUBSTANCE, Low molecular weight heparin, Fragmin®.

Names

INN (WHO list 31), BAN	Dalteparin sodium
Trade name	FRAGMIN® drug substance
Laboratory code and names	- Heparin fragment Kabi 2165 - Low molecular weight heparin (sodium salt)
Chemical name	Oligo-saccharides derived from heparin, major components are 2-O-sulfo-α-L-idopyranosuronic acid at the non-reducing end and a 6-O-sulfo-2,5-anhydro-D-mannitol at the reducing end of the chain. Average molecular mass, 5000.

Physical, Chemical and Biological characteristics

Description:

An odorless white or yellowish white powder moderately hygroscopic and freely soluble in water.

Solubility/Viscosity:

1 gm per ml of water yields a viscosity of 314 mPas.

pH:

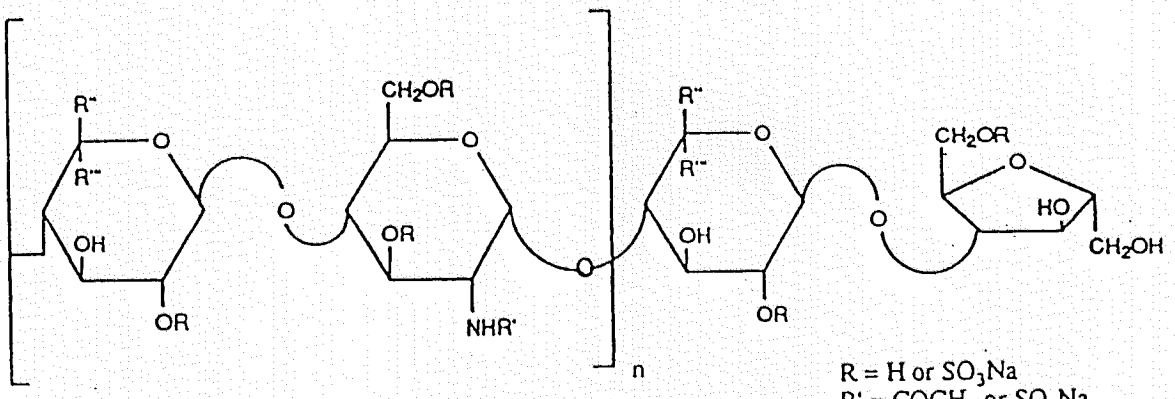
1 % w/w solution of the sodium salt has a pH of 5.0 - 7.5.

Optical rotation:

The specific optical rotation is not less than

$[\alpha]\ D^{20} = +35^{\circ}$ (C = 2.0, water).

Structural formula:



R = H or SO_3Na
R' = $COCH_3$ or SO_3Na
R" = H R'" = COONa
or
R" = COONa R'" = H

n = 3-20

Molecular formula:

C, H, O, N, and S with variable composition.

Relative molecular mass:

Polydisperse, with about 90 % of the material within 2000 - 9000 and with an average of 5000.

Biological Activity/Potency:

1. Anti-Factor Xa activity (Method of Analysis, H-236)

   One International Unit (anti-Factor Xa) of Fragmin corresponds to the activity of one International Unit of the First International Standard for low molecular weight Heparin with respect to inhibition of coagulation Factor Xa in plasma utilizing the chromogenic substrate S-2222.

2. APTT activity (Method of Analysis, F-601)

   One International Unit (APTT) of Fragmin corresponds to the activity of one International Unit of the First International Standard for low molecular weight Heparin with respect to its ability to prolong the plasma clotting time as measured by the APTT assay.

3. Coagulation Factor IIa assay (Method of Analysis, S 643)

   One International Unit (anti-Factor IIa) of fragmin corresponds to the activity of one International Unit of the First International Standard for low molecular weight Heparin with respect to inhibition of thrombin by purified antithrombin utilizing the chromogenic substrate S-2238.

Specific activity:

The specific activity of Fragmin as measured by the anti-Factor Xa activity is about 160 IU/mg.

The specific activity of Fragmin as measured by the APTT and anti-Factor IIa activity is about 60 IU/mg.

The ratio anti-Factor Xa activity is (IU/mg) per APTT activity (IU/mg) is about 2.6.

Items 6, 7, 9, 10 and 11, namely, - Item 6, Introduction of substances into the environment; Item 7, Fate of emitted substances in the environment; Item 9, Use of resources and energy; Item 10, Mitigation measures; and Item 11, Alternatives to the proposed action, - are addressed in the enclosed document from the Swedish National Franchise Board, decision number Dnr 502-180/88 and a statement from Kabi Pharmacia regarding Vetter Pharma Fertigung, GmbH & Co KG. See appendix, document 1.

Item 8.) Environmental effects of released substances;

This information is partially address in the Swedish National Franchise Board document cited above as well as this New Drug Application Volumes 1.7 to 1.10, - Nonclinical, pharmacology, and toxicology section. See appendix document 2 for summary.

Item 12.) List of preparers;

1. Dr. Ronald G. Leonardi, Ph.D.
   President, R & R REGISTRATIONS
   P.O. Box 262069
   San Diego, CA 92196-2069
   Curriculum Vitae, see appendix 3.

2. Mr. Claus-Gunnar Meinking
   Plant Manager
   Kabi Pharmacia AB, Biopharma
   S645 41 STRÄNGNÄS, Sweden
   Curriculum Vitae, see appendix 3.

3. Mr. Anders Ulfhielm
   Vice President, Operations
   Kabi Pharmacia AB, Biopharma
   S112 87 STOCKHOLM, Sweden
   Curriculum Vitae, see appendix 3.

Item 13.) Certification;

The undersigned officials certify that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the environmental assessment.

DATE.....; Signature(s) and Titles

Dr. Ronald G. Leonardi, Ph.D.
President, R & R REGISTRATIONS

Mr. Claus Gunnar Meinking
Plant Manager
Kabi Pharmacia AB, Biopharma

Mr. Anders Ulfhielm
Vice President, Operations
Kabi Pharmacia AB, Biopharma

Item 14.) References;
Fragmin New Drug Application, enclosed.

Item 15.) Appendices;

1. Environmental assessment statements for [redacted]
2. NDA Pharmacology-Toxicology Summary
3. Curriculum Vitae of preparers

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Appendix 2

FONSI dated 3 March 1993 written for Original EA dated 1 March 1992

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-287

Fragmin (dalteparin sodium)

Injection

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Fragmin, Kabi Pharmacia AB has conducted a number of environmental studies and prepared an environmental assessment (21 CFR 25.31a(a)(5) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Fragmin, a low molecular weight heparin, acts mainly by accelerating the rate of neutralization of certain activated

coagulation factors by antithrombin.

The drug substance is manufactured in Sweden. The drug product is manufactured in Germany. The firm has provided letters from the appropriate government officials with specificity to the drug asserting that manufacture will not have a significant environmental impact. The Agency believes that use and disposal of the drug product will not have significant environmental impact due to the biological nature of the altered heparin molecule.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Any residues of Fragmin or its major metabolites entering the environment as a result of administering the drug to humans are expected to rapidly degrade.

3/3/93
DATE

Phillip G. Vincent, Ph. D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

3/3/93
DATE

Charles S. Kumkumian, Ph. D.
Assistant Director (Chemistry)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
MSDS
FPL

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Appendix 3

MSDS for the Drug Product, FRAGMIN

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Appendix 3

MATERIAL SAFETY DATA SHEET

Revision Date: March 27, 1995
Agent Id#: 53875

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

COMMON NAME: FRAGMIN®
SYNONYMS: Dalteparin Sodium Injection
MOLECULAR FORMULA: Mixture
MANUFACTURER/SUPPLIER: PHARMACIA & UPJOHN
7171 PORTAGE RD
KALAMAZOO, MI 49001-0199
TELEPHONE NUMBERS: (616) 833-5122 - (24 HOURS)
(616) 833-7555 - (8:00 a.m. - 4:30 p.m.)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENT 1
COMMON NAME: Water
% BY WEIGHT: 89 - 94 %
CAS NUMBER: 7732-18-5
EXPOSURE LIMIT(S): Not established.

INGREDIENT 2
COMMON NAME: Heparin Sodium
% BY WEIGHT: 5.9 - 11.4 %
CAS NUMBER: 9041-08-1
EXPOSURE LIMIT(S): Not established.
EXPOSURE LIMIT(S) FOR THE MATERIAL: Not established.

INGREDIENT 3
COMMON NAME: Sodium Chloride
% BY WEIGHT: < 1%
CAS NUMBER: 7647-14-5
EXPOSURE LIMIT(S): Not established.

3. HAZARDS IDENTIFICATION

PRIMARY ROUTE(S) OF EXPOSURE: Inhalation, ingestion, absorption through the skin or accidental needle puncture injury.
EFFECTS OF OVEREXPOSURE:
ACUTE OVERXPOSURE: Bleeding.
CHRONIC OVEREXPOSURE: Bleeding.
MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Bleeding, diathesis.

4. FIRST AID MEASURES

EYES: Rinse with water. Assure adequate flushing by separating the eyelids with fingers. Seek medical attention if irritation persists.
SKIN: Wash with soap and water.
INHALATION: Move to fresh air, rest. Rinse nose and mouth with water. Get medical attention immediately. If breathing becomes difficult, call a physician.
INGESTION: Wash out mouth with water. Give some glasses of water.

5. FIRE FIGHTING MEASURES

FLASH POINT: Not applicable.
LOWER EXPLOSION LIMIT (LEL): Not applicable.
UPPER EXPLOSION LIMIT (UEL): Not applicable.
AUTOIGNITION TEMPERATURE: Not applicable.
EXTINGUISHING MEDIA: Water spray, carbon dioxide, dry chemical powder, or polymer foam as appropriate for surrounding fire and materials.
FIRE-FIGHTING PROCEDURES: Evacuate personnel to safe area. Fire-fighters should use self-contained breathing equipment and protective clothing.
UNUSUAL FIRE OR EXPLOSION HAZARDS: None.
HAZARDOUS COMBUSTION PRODUCTS: Unknown.

6. ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED: Use NIOSH/MSHA-approved mask for protection from aerosols. Swab with absorbent wipes, paper towel, cellulose sorbent, vewrmiculite or the like. Place the absorbent material into a plastic bag and dispose of in accordance with Federal, state and local regulations.

7. HANDLING AND STORAGE

PRECAUTIONS FOR HANDLING AND STORING: Handle with care. Avoid formation of aerosols. Store in original packing (single dose syringes in cartons) at room temperature.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

RESPIRATORY PROTECTION: Wear suitable respiratory equipment, NIOSH/MSHA-approved for protection from aerosols.
VENTILATION: General.
PROTECTIVE GLOVES: Yes.
EYE PROTECTION: Safety glasses.
OTHER PROTECTIVE EQUIPMENT: Not applicable.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE/PHYSICAL STATE: Clear, colorless or straw-colored solution.
BOILING POINT: The product consists of approximately 90% water. The value is essentially the same as water.
EVAPORATION RATE: The product consists of approximately 90% water. The value is essentially the same as for water.
MELTING POINT: Not applicable.
SOLUBILITY IN WATER: Freely soluble.
SPECIFIC GRAVITY (WATER=1): 1.04
VAPOR DENSITY (air = 1): The product consists of approximately 90% water. The value is essentially the same as for water.
VAPOR PRESSURE: The product consists of approximately 90% water. The value is essentially the same as for water.
VOLATILITY: Product is 89-94% water.
REACTIVITY IN WATER: None.

10. STABILITY AND REACTIVITY

STABILITY: Stable.
PHYSICAL CONDITIONS TO AVOID: None.
INCOMPATIBILITY WITH OTHER MATERIALS: None.
HAZARDOUS DECOMPOSITION PRODUCTS: None.
HAZARDOUS POLYMERIZATION: Will not occur.

11. TOXICOLOGICAL INFORMATION

ACUTE STUDIES:
INTRAVENOUS LD50 (DOG): 1,000 MG/KG
INTRAVENOUS LD50 (RAT): 354 MG/KG
INTRAVENOUS LD50 (MOUSE): 2,800 MG/KG
ORAL LD50 (MOUSE): > 5,000 MG/KG
INTRAPERITONEAL LD50 (MOUSE): > 2,500 MG/KG
SUBCUTANEOUS LD50 (MOUSE): > 2,500 MG/KG
OTHER STUDIES:
CARCINOGENICITY: Ingredient(s) are not listed as carcinogenic by IARC, NTP or OSHA.

12. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHOD: Mix the material with a combustible solvent and burn in a chemcial incinerator equipped with an afterburner and scrubber. Dispose of in accordance with federal, state and local regulations.

13. OTHER INFORMATION

DISCLAIMER: The MSDS information is believed to be correct but should only be used as a guide. Pharmacia & Upjohn disclaims any express or implied warranty as to the accuracy of the MSDS information and shall not be held liable for any direct, incidental or consequential damages resulting from reliance on the information.

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Appendix 4

Ingredients Used in Formulating the Drug Product

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Appendix 4

Ingredients Used in Formulating the Drug Product

Ingredient	CAS No.	M.W.	Formula	Physical Appearance
Dalteparin sodium	9041-08-1	Avg. molecular mass: 5000 D	Not applicable: depolymerization of sodium heparin	White or yellowish-white powder
Sodium chloride*	7647-14-5	58.44	NaCl	White powder
Water	7732-18-5	18.0	H_2O	Colorless liquid

*applicable to 2500 IU/0.2 mL, single-dose syringes

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Appendix 5

Compliance Letter - Sweden

Pharmacia & Upjohn

Food and Drug Administration
CDER
Rockville, MD
USA

Strängnäs, June 2, 1997

HABO/LEIL

Pharmacia & Upjohn AB certifies that its manufacturing facilities for the production of dalteparin sodium are in compliance with all local and national environmental laws; are in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and that approval and subsequent increase in production at the facility are not expected to affect compliance with current emission requirements of compliance with environmental laws.

Yours sincerely,

PHARMACIA & UPJOHN AB
Technical Operations
Plant Strängnäs

Börje Haag
Plant Manager

Postal address
Pharmacia & Upjohn AB
Strängnäs Plant
S-645 41 Strängnäs
Sweden

Office address
Marlefredsvägen 37

Telephone
+46 152 273 00

Telefax
+46 152 273 66

Registered Office: Stockholm. Reg. No.: 556131-9608

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Appendix 6

Compliance Letter - Germany

[redacted]

[redacted]

[redacted]

Name: [redacted]

[redacted]

Food and Drug Administration
CDER
5600 Fishers Lane
ROCKVILLE, MD 20857
U.S.A.

Date: **June 3, 1997**

Environmental Assessment

[redacted] certifies that its manufacturing facilities for the production of **FRAGMIN (dalteparin sodium) Injection**

- are in compliance with all local and national environmental laws;
- are in compliance with, or are on an enforceable schedule to be in compliance, with all emission requirements set forth in all permits;
- and that approval and subsequent increase in production at the facility are not expected to affect compliance with current emission requirements or compliance with environmental laws.

/S/ [redacted]
Managing Director

/S/ [redacted]
Director of Regulatory Affairs

[redacted]